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4,6-BIS(IMIDAZOLIO)PYRIMIDINE AS A NEW ANION RECEPTOR

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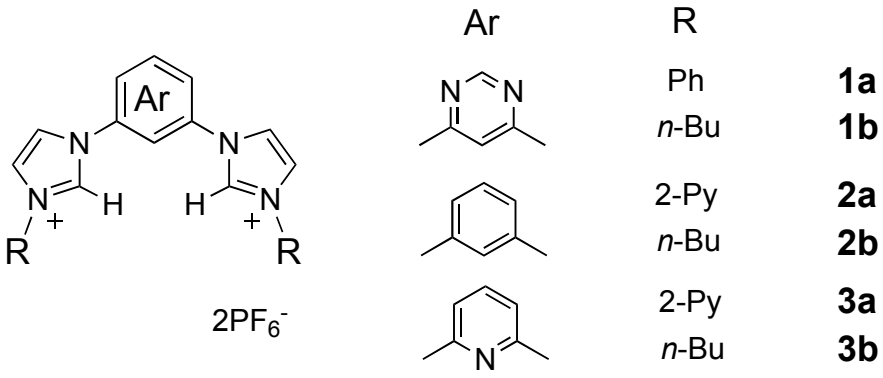
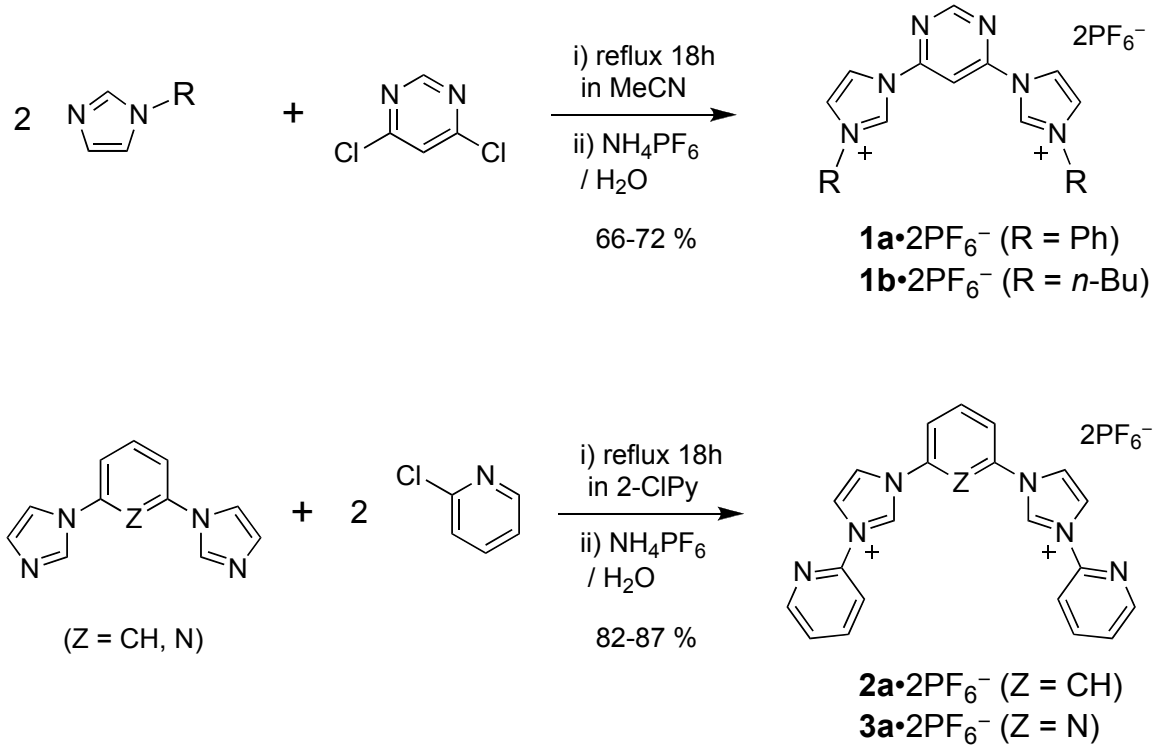
Abstract – New aryl-oligomer type anion receptors bearing two imidazolium units linked by 6-membered ring aryl spacers at *meta*-positions have been synthesized. Complexation behavior of the receptors with halide ions (Cl^-, Br^-, and I^-) in DMSO-d_6 was investigated by ^1H NMR titrations and semi-empirical calculations (MOPAC AM1). Along with the imidazolium C-H protons, the *ortho* C-H proton of the central aryl unit forms additional hydrogen bond interaction with guest anion. The receptor with pyrimidine unit exhibited significantly improved anion binding properties.

INTRODUCTION

Anion recognition chemistry by synthetic receptors had been slow to develop compared to cation recognition, but the field of research has expanded rapidly in the last two decades, and several classes of receptors, which include different hydrogen-bonding groups, have been designed to specific anions.[1] In 1999 we have reported that imidazolium group acts as a new efficient binding subunit for anions through electrostatic and C-H ••• X^- type hydrogen-bonding interactions, and the receptors incorporated this cationic heterocycle show strong binding ability for small inorganic anions in polar solvents.[2] Since then, imidazolium-based anion receptors are becoming increasingly common now.[3] However, in most receptors, imidazolium groups are connected to a scaffold by flexible methylene spacers. Removal of methylene spacers from those receptors would be expected to increase rigidity of binding site and affinity to guest anion. Thus, we designed new aryl-oligomer type receptors (**1-3**), in which two imidazolium units are directly linked to 6-membered ring aryl spacers at *meta*-positions.



The receptor **1a** was prepared according to Scheme 1. Reaction between one equivalent 4,6-dichloropyrimidine and two equivalents of 1-phenylimidazole[4] in acetonitrile afforded 1,1'-(pyrimidine-4,6-diyl)bis(3-phenyl-1*H*-imidazol-3-ium) dichloride (**1a**•2Cl$^-$). After counter ion exchange by NH_4PF_6, the bis(hexafluorophosphate) salt (**1a**•2PF_6^-) was obtained in 66% yield.[5] The bis(butylimidazolium) analogue (**1b**•2PF_6^-) was also obtained in 72% yield from 1-butylimidazole and 4,6-dichloropyrimidine. The receptors **2a** and **3a** were synthesized by refluxing 2-chloropyridine solutions of 1,3-diimidazolylbenzene and 2,6-diimidazolylpyridine, respectively (Scheme 1). The other receptors **2b** and **3b**, known as precursors of 'pincer' type N-heterocyclic biscarbene ligands, were prepared according to literature methods [6,7] followed by counter ion exchange.



Scheme 1. Synthesis of the receptors **1a, 1b, 2a,** and **3a.**

The anion binding properties of the receptors were investigated using ^{1}H NMR titration.[8] Addition of increasing amounts of tetrabutylammonium chloride to a DMSO-d_6 solution of **1a**•2PF_6^- (4 mM) leads to significant downfield shift of the C(2)-H of imidazolium (Im-2) due to the formation of C-H ••• X^- type hydrogen bonded complex[2,3] (Figure 1). The C(5)-H of imidazolium (Im-5) also moves to downfield due to positional interchange of the C(2)-H (Im-2) with the C(5)-H (Im-5) by rapid rotation about the Pym-Im C-N bond (Scheme 2). Interestingly, the C(5)-H of pyrimidine ring (Pym-5) shows more drastic chemical shift change from 8.90 ppm to 10.05 ppm (at 2 equiv. addition of chloride ion). Meanwhile, the peak of the C(2)-H of pyrimidine (Pym-2) does not show any downfield shift but slightly upfield shift. These results strongly suggest that the guest anion locates in the pocket of the receptor **1a** (Scheme 2).

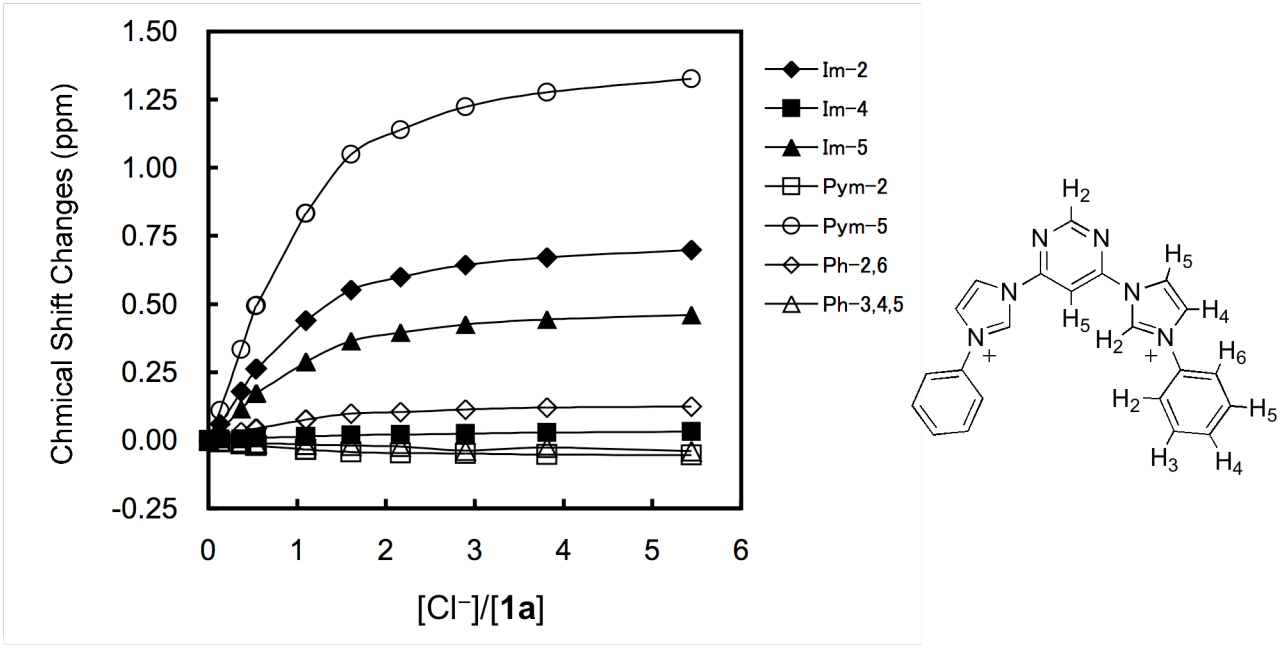
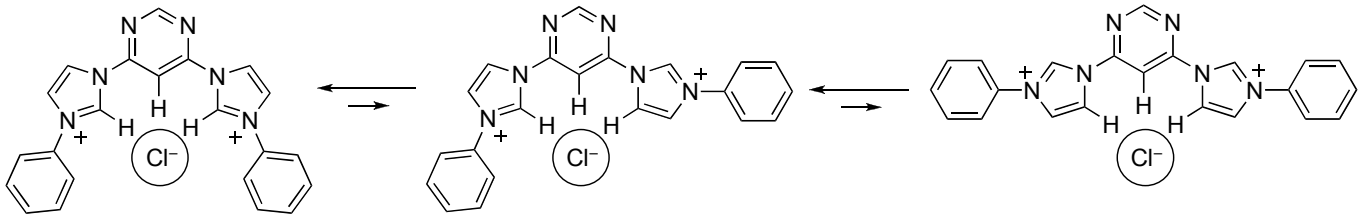


Figure 1. ^{1}H NMR chemical shift change of the receptor **1a** (4 mM in DMSO-d_6) by addition of tetrabutylammonium chloride.



Scheme 2. Possible anion binding modes of the receptor **1a**.

The association constants of the receptors **1-3** and halide ions in DMSO-d_6 solution were calculated from the chemical shift change by non-linear least square curve-fitting assuming a 1:1 complex and are shown in Table 1.

Table 1. Association constants $\boldsymbol{K_a}$ (M^{-1}) for 1:1 complex of the receptors **1-3** with halide anions (as tetrabutylammonium salts) determined by ^{1}H NMR titration in DMSO-d_6 at 298 K.

Receptor	**1a**	**2a**	**3a**	**1b**	**2b**	**3b**
Cl^-	690	74	71	270	88	90
Br^-	120	57	41	110	39	48
I^-	41	– [b]	– [b]	34	– [b]	– [b]

[a] Errors are estimated to be < 10%.

[b] No significant shift was observed. ($\boldsymbol{K_a}$ < 20 M^{-1})

All receptors show similar guest selectivity $Cl^- > Br^- > I^-$, which reflects the relative hydrogen-bonding ability and surface charge density of the anions. However, a comparison of the association constants of the oligo-aryl receptors **1a**-**3a** shows that the anion binding affinity of the bis(imidazolio)pyrimidine **1a** is higher than that of **2a** and **3a**, suggesting that the electronic effect of central aryl ring, directly connecting to the imidazolium rings, plays an important role. Compared with benzene and pyridine rings, more electronically deficient pyrimidine ring acts as a strong electron-withdrawing group that should enhance hydrogen bonding ability of the imidazolium units. A similar improvement by pyrimidine ring was observed in the butyl analogous **1b-3b**. Additionally, the *ortho* C-H proton (Pym-5) of the central pyrimidine ring of **1a,b** showed significant downfield shifts during NMR titration. The large chemical shift changes are presumably due to the additional hydrogen bond of the C-H proton (Pym-5) that would also contribute for the stability of the host-guest complexes with **1a** and **1b**.

Molecular modeling study (MOPAC, AM1) evaluated the detailed structural information on the host-guest complex. The lowest-energy conformation of the complex **1a•Cl$^-$** is shown in Figure 2 (left). Although the central pyrimidine ring is slightly deviated from the plane of the neighboring imidazolium rings (ca. 16-18°), the three aryl rings are almost co-planer and the chloride anion closely contacts with three C-H protons of the imidazolium and pyrimidine rings. The average distance between the imidazolium C-H protons (Im-2) and chloride is 1.799 ± 0.004 Å and the average of the C-H ••• Cl^- angles is 169.9 ± 1.1°, indicating the presence of strong hydrogen bonds, while optimized distance between the C-H proton (Pym-5) and chloride and the C-H ••• Cl^- angle are 2.097 Å and 144.4°,

respectively. These values also supported the additional C-H ••• X^- hydrogen bonding interaction between the pyrimidine ring and guest anion.[9] Similar experimental observations and theoretical calculations of additional aryl C-H ••• X^- hydrogen-bonds on anion binding were recently reported by several groups.[10-13] Furthermore, the crystal structure analysis of 1,3-bis(2-pyridyl)imidazolium chloride[14] revealed that the chloride ion forms weak hydrogen bonds with C(3)-H protons of the pyridine rings in addition to the imidazolium C(2)-H proton in the crystalline state.

The optimized structure of **2a•Cl⁻** (Figure 2, right) is essentially the same as **1a•Cl⁻** except that the central benzene ring is further tilted (ca. 29-30º). The distance between the benzene C-H proton and chloride anion (2.379 Å) is much longer and the C-H ••• Cl^- angle (126.6º) is much smaller than the corresponding values of **1a•Cl⁻**. These geometrical parameters allow only weak hydrogen bonding interaction. This is consistent with the results of the NMR titration study. The *ortho* C-H proton of the benzene bridged receptors (**2a** and **2b**) also shifted to downfield by addition of halide ions, but the observed chemical shift changes were less than half of the corresponding pyrimidine C-H (Pym-5) proton chemical shift changes of **1a** and **1b**.

On the other hand, in the case of the pyridine bridged receptors (**3a** and **3b**), the central pyridine ring is not efficient for anion binding. The association constants of **3a** and **3b** are similar to those of **2a** and **2b**. The electron-withdrawing effect of the pyridine rings on the hydrogen bonding ability of imidazolium units is probably canceled out by the electrostatic repulsion between lone-pair of the central pyridine ring and the guest anion. Similar destabilizing effects of the lone-pair of pyridine scaffolds on binding anionic guests are reported.[15]

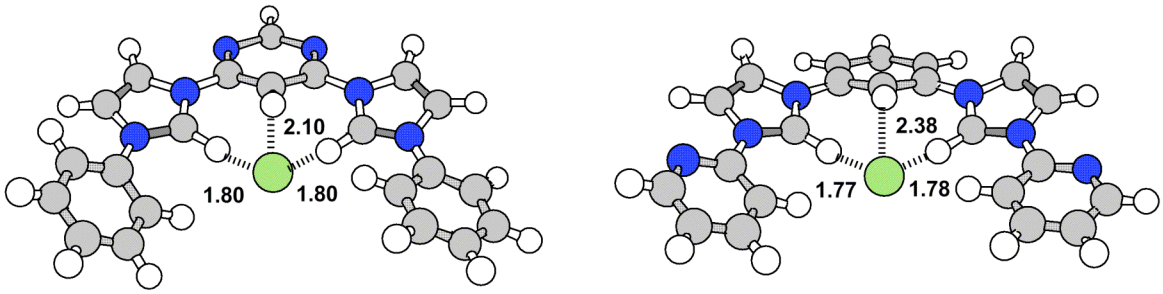


Figure 2. Calculated lowest-energy conformation (MOPAC, AM1) of the 1:1 complexes between chloride and the receptor **1a** (left) and the receptor **2a** (right).

In conclusion, we have designed and synthesized a series of novel imidazolium-aryl co-oligomers with different central aryl units for anion recognition. ^{1}H-NMR titration study and semi-empirical calculations (MOPAC AM1) reveal that the anion binding properties of the new aryl-oligomer type receptors are

significantly affected by both of the electronic nature and the additional C-H ••• X^- interaction of the central aryl unit. The 4,6-bis(3-phenyl-1-imidazolio)pyrimidine **1a** is an example for a new class of imidazolium-based multiple C-H ••• X^- hydrogen bonding anion receptor. There would be promising further developments for novel aryl-oligomer type anion receptors. We are currently exploring the imidazolium-based macrocyclic and podand (non-macrocyclic) systems.

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